Werner's syndrome and acute myeloid leukemia

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Werner's syndrome was first described by Otto Werner[1] in 1904. He reported a family of two brothers and two sisters who had the appearance of premature ageing. Although only in their twenties, they had loss and greying of hair, cataracts and pinched facial features. In addition there were "scleroderma-like" skin changes of their feet. Since Werner's original report, 136 such cases have been recorded in the literature.[2-5] Most patients have been of European, Jewish or Japanese ancestry.

Most of the major clinical manifestations of Werner's syndrome do not appear until the second and third decades, and the average age at death is 47 years.[2] The two principal causes of death are vascular accidents involving the coronary and cerebral arteries, and malignancy. Malignancy occurred in 14 of the 136 recorded patients. This incidence of about 10% suggests an increased susceptibility.

Our purpose in this paper is to describe the autopsy findings of a patient with this rare disease who developed acute myeloid leukemia as a terminal event. Tissue culture and cytogenetic studies were also performed.

Case history

Our patient (M.P.) was a white woman born in 1945 who died at 24 years of age. Aside from the usual illnesses she was in good health throughout her childhood. She completed grade nine in school and worked in a hospital as a nurses' aide. In 1965, at 20 years of age, she underwent removal of both lenses because of cataracts, at Women's College Hospital, Toronto. During this admission she was discovered to be mildly diabetic with a slightly raised systolic blood pressure (140-150 mm. Hg). Further investigation of these problems had to be deferred because she became pregnant. A spontaneous abortion terminated the pregnancy at 19 weeks.

Nothing further was done until May 1968, when she was investigated at the Toronto General Hospital. She was described as lean and emaciated, with "pinched" facies. There was evidence of muscle atrophy in all her extremities as well as a striking loss of subcutaneous tissue. Her blood pressure was 160/80. Mild diabetes was easily controlled by dietary measures. Her ESR was 65 mm. in the first hour. LE cells could not be demonstrated. Hematologic studies were normal. Although the working diagnosis was a collagen disorder, no conclusions were reached.

She was readmitted one year later, in April 1969. During the previous two weeks she had become short of breath on exertion, and within the preceding few days she had had recurrent nose bleeds, profuse vaginal bleeding and spontaneous bruising. Her hemoglobin was 5.5 g. per 100 ml. and the platelet count was 20,000 per c.mm. Her total leukocyte count was 9700 with 17% neutrophils, 6% lymphocytes, 9% metamyelocytes, 28% myelocytes, 25% promyelocytes and 10% blasts. Two bone marrow aspirations were unsuccessful, and a posterior iliac crest bone biopsy was performed; this showed an extremely hypercellular marrow with a marked increase in primitive cells, establishing a diagnosis of acute leukemia. She was treated with blood transfusion, prednisone (which induced a remission), and a cyclic estrogen-progesterone preparation (which controlled her vaginal bleeding).

It was during this admission that the diagnosis of Werner's syndrome was recognized. The marked alteration of facial features which had occurred between 1964 and 1969 can be seen in Figs. 1a and 1b.

Her last admission to Toronto General Hospital on October 17, 1969, was necessitated by recurrent epistaxis, vaginal bleeding, and ulcers on her left leg and in the perineal region. Uterine curettage was performed to control her vaginal bleeding, and examination of the endometrium showed leukemic infiltrate of the myeloid series. Blast cells in her peripheral blood rose to 40%. 6-Mercaptopurine and vincristine had no effect on her course and she died on November 13, 1969.

Family history

The parents of M.P. were second cousins once removed (Fig. 2). The family is large and includes four paternal uncles, four paternal first cousins, eight maternal uncles, one maternal aunt and 16 maternal first cousins. No other member of the patient's family has Werner's syndrome. One maternal uncle has diabetes. Both the father and the brother of the patient had thinning of the hair at an early age. Neither premature greying of the hair nor cataracts were present in other members of the family.

Autopsy findings

The patient was 157 cm. tall and weighed 41 kg. She appeared older than her stated age, with a sharp pinched facies, parchment-like skin and subcutaneous and muscle atrophy of her extremities. Cutaneous ulcers were present on her legs and perineum. There was relatively good preservation of abdominal fat. Her scalp hair was not grey nor was there baldness.

The bone marrow was packed with leukemic cells. Their nuclei had fine chromatin and contained two to six nucleoli. Some cells exhibited a fine paranuclear granularity. These features are compatible with primitive cells of the myeloid series. The spleen (Fig. 3), lymph nodes, liver, lungs, kidneys, uterus and skin all showed leukemic involvement.

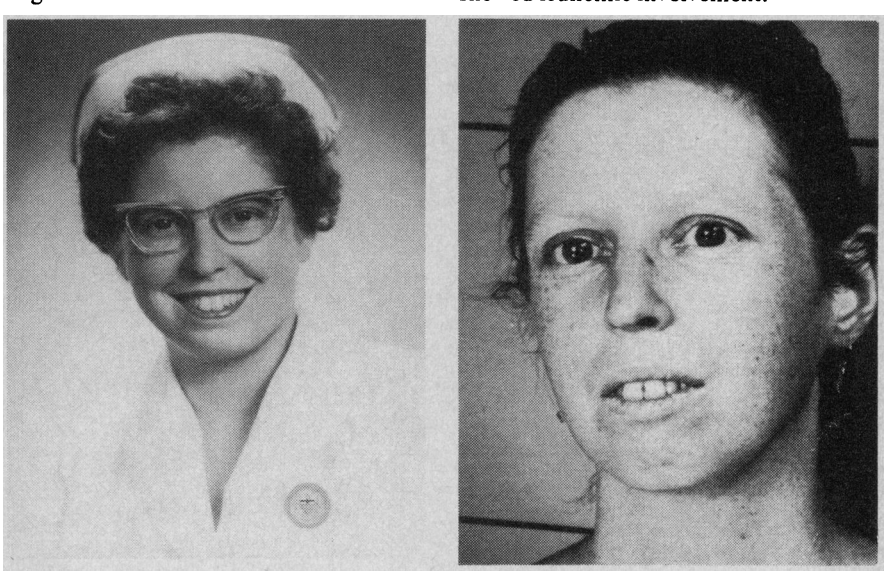

FIG. 1—(a) The natural appearance of the patient in 1964 is contrasted with (b) the "Werner's appearance in 1969. The thin, "pinched" facial features of Werner's syndrome are well demonstrated.

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Atherosclerosis was present in all major arteries, but except in the coronary arteries the changes were mild, being manifested by fatty streaks. The coronary arteries showed areas of pronounced plaque formation.

Sections of skin taken from the leg showed flattening of the rete ridges and fibrous replacement of the dermis. The number of hair follicles and other appendages were decreased. The adrenal gland showed hyperplasia of the zona glomerulosa. Sections of ovary showed a corpus luteum, a few corpora albicantes and a number of primary follicles. No developing follicles were present.

The brain weighed 1120 g.—slightly less than a normal brain at this age. There were no pathologic abnormalities to be seen. The basophils of the pituitary showed Crooke's hyaline change, the result of prednisone therapy.

Cytogenetic and tissue culture studies

Chromosome analyses were performed on several occasions. All cultures were grown in Media TC 199 (Hyland) supplemented with 20% fetal calf serum, penicillin and streptomycin, heparin and phytohemagglutinin (PHA).

On April 25, 1969, 10 cells from a peripheral blood culture were examined at The Hospital for Sick Children, Toronto, and two karyotypes were made. On June 10, 1969, peripheral blood was cultured at Toronto General Hospital. Ten cells in metaphase were analyzed. At autopsy on October 24, 1969, blood was taken and leukocyte-rich plasma was cultured. Twenty-eight cells were analyzed and two karyotypes were made. Thus a total of 48 cells from peripheral blood were examined. The basic chromosome pattern was that of a normal woman, 46, XX. Other cultures incubated without PHA also had a 46,XX pattern, and no chromosome abnormalities related to the acute leukemia were found.

Fiver coverslip cultures in Leighton tubes were prepared from skin taken at autopsy three hours after death. The lag period preceding the beginning of growth was very long—30 days. Following this there was a slow but definite proliferative phase, so that enough cells were present by day 55 for subculturing. Although the cells settled and seemed to adhere well to the new coverslips, growth was poor, and by day 90 the three subcultures were degenerating. Attempts to obtain metaphase preparations for chromosome studies were unsuccessful.

At the time these skin cultures were initiated it was not possible to set up a matched control. The cultural characteristics were therefore compared with those of other autopsy and biopsy skin fibroblast preparations initiated during this same period of time, handled in the same manner and using the same media. These cultures had evident growth within five to 10 days, subcultures being possible at 10- to 14-day intervals for many months.

Discussion

Werner's syndrome and premature ageing have many features in common and have frequently been confused. Atherosclerosis, greying and loss of hair, and dermal and subcutaneous atrophy are present in both conditions. On the other hand there are features which are characteristic of Werner's syndrome and distinguish it from ageing.

The many family studies which have been reported seem to establish fairly certainly that Werner's syndrome is inherited in an autosomal recessive manner. Although this illness does occur sporadically, many patients are the products of consan-

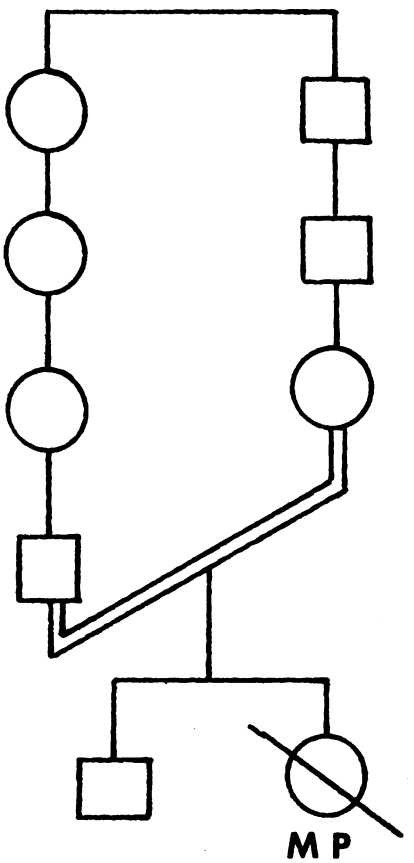

FIG. 2—Abridged pedigree of M.P. The patient's parents were second cousins once removed.

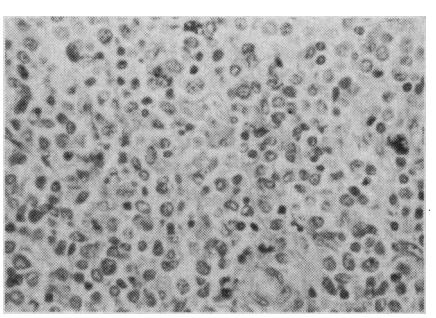

FIG. 3—Microphotograph of spleen illustrating infiltration by primitive myeloid cells (H. & E., X600.)

guineous marriages,[6-12] as was true of our patient.

It has been suggested that in the family of a patient who has Werner's syndrome, diabetes or early thinning of the hair with or without premature greying represents a variant of this illness or its heterozygous state.[2, 3] We find it difficult to come to this conclusion. Diabetes was present in one uncle of the patient. However, diabetes itself is a familial disease and is common in the community. The same is true of premature balding (present in the father and brother) and greying. We therefore cannot establish these traits as indicative of a variant or the heterozygous state of Werner's syndrome.

The early and abrupt appearance of cataracts, as occurred in our patient, is characteristic of Werner's syndrome. Cataracts usually appear before the age of 40 and begin as homogeneous or striate opacities in the subcapsular, cortical and posterior zones of the lens.[13] The cataracts of normal ageing begin in the nuclear region of the lens.

Generalized and early atherosclerosis is reported as being prominent in Werner's syndrome.[2] Severe atheromatous changes were observed in our patient's coronary arteries but only fatty streaks were present in the other major vessels.

Hypogonadism and maturity-onset diabetes are common endocrine problems. Small breasts and ovaries were present in this patient but there was no evidence of oligomenorrhea or early menopause. The incidence of diabetes in Werner's syndrome is 45%. It is usually mild, but unresponsive to insulin. Our patient's diabetes was mild and diet proved effective in controlling it; insulin was not required. The zona glomerulosa of the adrenal gland is wider in Werner's syndrome than is found normally.[2] This was true in this patient.

The most salient clinical manifestation of Werner's syndrome is the subcutaneous atrophy, and this was well documented in our patient. Involvement of the face caused the skin to mould to the bony contours, giving her a thin, sharp, "pinched" appearance. The skin of the extremities was shiny, thin and parchment-like, and there were trophic ulcers on her legs. The underlying musculature was atrophic.

The finding of a normal chromosome complement in our patient agrees with previous observations.[2, 7, 13-18] Few reports describe the characteristics of cultured fibroblasts, but our observations are consistent with the one study which has been published.[2, 19, 24] The fibroblasts are less efficient in establishing growing colonies than normal cells, and once established few subcultures can be undertaken before the culture degenerates.[24]

The 136 patients with Werner's syndrome recorded in the literature show a high incidence of neoplastic disease. Fourteen cases with malignant tumours have been reported. Seven had a sarcoma: fibrosarcoma,[3, 8] fibroliposarcoma,[20] osteogenic sarcoma,[4, 7, 20] sarcoma of nerve sheath origin,[7] leiomyosarcoma[21] or spindle-cell sarcoma.[22] Seven had a carcinoma: cholangiocarcinoma,[12] liver cell carcinoma,[3, 8, 20] carcinoma of breast,[9] papillary carcinoma of thyroid[6] or malignant melanoma.[10] Solitary meningiomas were found in two patients,[12, 23] and multiple meningiomas in a third patient.[3] Adenomas of the thyroid and adrenals were noted in several patients,[2] as well as a leiomyoma of the uterus in a 26-year-old woman.[11] One patient had a hemangiolipoma with occasional mitoses.[14]

Our patient appears to be the first case associated with leukemia. Neither the type of leukemia (acute myeloblastic), its course (seven months) nor the age of onset (24 years) seemed in any way affected by her Werner's syndrome.

We are very grateful to Dr. Diane W. Cox, Department of Genetics, The Hospital for Sick Children, Toronto, for her help in gathering a comprehensive family study on this patient and reviewing the manuscript. We also thank Dr. A. C. Ritchie and Dr. C. Ezrin for their comments and criticisms.

Summary:

A 24-year-old white woman with Werner's syndrome developed acute myelogenous leukemia. The autopsy findings are described. Tissue culture studies indicated abnormalities of *in vitro* fibroblast growth. Cytogenetic studies of peripheral blood lymphocytes revealed a normal female chromosome pattern of 46,XX. The disease is inherited as an autosomal recessive, but its pathogenesis is not known.

There is a relatively high incidence of neoplastic disease in patients with Werner's syndrome. Fourteen of 136 cases recorded in the literature are associated with malignant tumours. This is the first recorded case in which leukemia developed.

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Erratum

The review of the book "My Brother's Keeper?" by Dr. Monnica C. Stewart (*Can Med Assoc J* 105: 411, 1971) mistakenly gives the impression that Dr. Lewis is the author of the second edition of this book. In the text of the review, the name Dr. Stewart should appear instead of Dr. Lewis. We regret the occurrence of this error.